Opportunities and pitfalls in colorectal cancer screening

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CHAPTER 6

Colonoscopy-controlled intra-individual comparisons to screen relevant neoplasia: Faecal Immunochemical Test versus Guaiac-based Faecal Occult Blood Test

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Abstract

Introduction: Guaiac-based Faecal Occult Blood Tests (g-FOBTs) are most commonly used in colorectal cancer (CRC) screening programs. Faecal Immunochemical Tests (FITs) are thought to be superior.

Methods: We assessed both sensitivity and specificity in different stages of CRC in eligible subjects who performed both FIT (OC-sensor®) and g-FOBT (Hemoccult-II®) prior to their scheduled colonoscopies.

Results: Of the 62 invasive cancers detected in 1821 individuals, g-FOBT was positive in 46 and FIT in 54 (74.2% versus. 87.1%, P=0.02). Among 194 patients with advanced adenomas, g-FOBT was positive in 35 and FIT in 69(18.0% versus 35.6%, P<0.001). 28 cancers were AJCC stage I or II, 31stages III or IV, and in 3 cases stage was indeterminate. Sensitivity for screen relevant tumors (197 advanced adenomas and 28 stage I or II cancers) was 23.0% for g-FOBT and 40.5% for FIT (P<0.001). Specificity of g-FOBT compared to FIT for the detection of cancer was 95.7% versus 91.0% (P<0.001), and 97.4% versus 94.2% for advanced adenomas (P<0.001).

Discussion: FIT is more sensitive for CRC and advanced adenomas compared to g-FOBT. Particularly, sensitivity of FIT for screen relevant tumors, early stage cancers and advanced adenomas, is significantly higher. Specificity of g-FOBT is higher compared to FIT.

Introduction

Colorectal cancer (CRC) is a leading cause of cancer death world wide. Early detection is one of the most realistic approaches to reduce CRC-related death. Guaiac-based faecal occult blood tests (g-FOBTs) were already proposed for this purpose in the early 1970s.(1) Blood, shed into the colonic lumen by colorectal adenomas and carcinomas yields a positive g-FOBT due to the peroxidase-like activity of haeme in stool.(2) Screening programs using g-FOBT have proven to reduce both incidence and mortality of CRC.(3-7) Yet, both clinical sensitivity (i.e. the percentage of tumours detected in a series of tumor positive patients that perform the test) and program sensitivity (i.e. the percentage of tumours present in a population intended to screen that actually is detected) are suboptimal.(8,9)

More recently, the Faecal Immunochemical Test (or FIT), has been introduced as an alternative to g-FOBT. The FIT selectively detects the human globin-protein in stool, making it specific to colonic blood loss, while globin from blood lost proximal to the colon will be degraded before entering the colon. (10,11) Several variants of FIT exist, some of which come with automated analysis and have quantitative outcomes, like the one used in the present study.(12)

Comparisons of different techniques to detect occult blood in stool have been performed since 1953.(13) Recent studies that compared g-FOBT and FIT in screening populations, indicated superiority of FIT for the detection of both cancers and advanced adenomas.(8,14,15) In order to evaluate whether FIT can replace the most commonly used test (g-FOBT) in CRC screening, a comparative study design is needed. Both g-FOBT and FIT should be performed in parallel on the same stool samples.(14-16)

In addition, in order to appraise specificity of a test directly, all test negative individuals should undergo the test that is considered the gold standard, colonoscopy. Inherent to the design of screening studies, only FOBT-positive individuals underwent colonoscopy.(8,14,15,17) A large scale comparison of g-FOBT and FIT in a colonoscopy controlled population is still lacking. In the present study, test characteristics of both tests could be determined directly, as colonoscopy was performed in all included participants.

While population based screening studies yield crucial information on program sensitivity and acceptance of a test in the target population, often only small numbers of colorectal cancers are detected.(18) Consequently, the power to stratify these cancers by stage is insufficient. (8,19) In a referral population, like in the present study, a higher prevalence of CRC and its precursor lesions will allow for stratification of FOBT result for different phases of the natural history of the disease.

Aim

Aim of the present study was an intraindividual comparison of test performance of a g-FOBT and a quantitative FIT for detection of colorectal cancers of all stages and advanced adenomas in a colonoscopy controlled population. In addition, a specific aim was to compare test performance of both tests for the detection of early stage cancers and advanced adenomas taken together, since these lesions are most relevant for screening .

Methods

Study population

Five hospitals in the Amsterdam area in The Netherlands participated in this study. From June 2006 to March 2008, all ambulatory patients ≥18 years, scheduled for colonoscopy were invited to participate in this study, regardless of the indication for colonoscopy. Two of these five participating hospitals are situated in rural areas, another two are large teaching hospitals with an urban population. One of the centres is an academic medical centre with a predominantly urban population. In all centers, local Medical Ethics Review Board approval was obtained prior to the start of the study, and informed consent was obtained from the participants.

Inclusion and exclusion criteria

All eligible individuals were asked to perform both types of FOBT in the week preceding colonoscopy. Neither patients who presented at an emergency room nor institutionalized patients were enrolled. All indications for colonoscopy, as stated by the referring physicians, were recorded. Patients with a documented history of Inflammatory Bowel Disease (IBD) or with an incomplete colonoscopy were excluded from further analysis, as were patients who failed to complete both tests.

Study design

Elective patients were invited to participate either by their gastroenterologist when visiting the outpatient clinic, or by telephone by one of five researchers based at each of the participating centres. Once a patient consented in participation, an envelop was sent to his/her home address containing background information on the study, both FOBTs with extensive instructions and an informed consent form. When a person could not be reached by telephone, the same package was sent but with an additional explanatory letter.

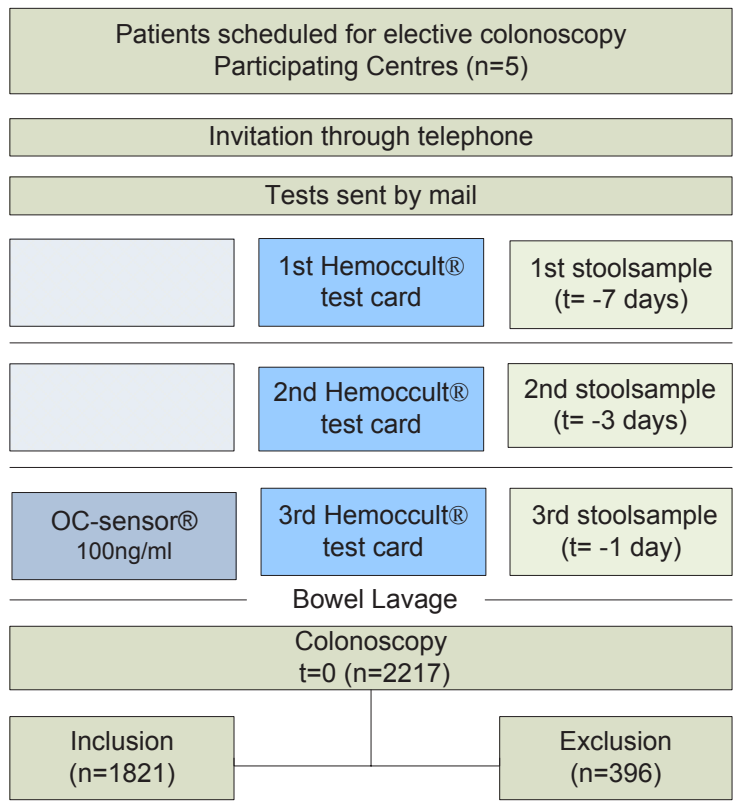
FOBTs

The tests compared were the widely used guaiac based FOBT; Hemoccult II® (Beckman Coulter Inc., Fullerton, CA, USA) and an automated quantitative faecal immunochemical test: OC-sensor® (Eiken Chemical Co., Tokyo, Japan).

Faecal sampling

The three test-cards of the g-FOBT were sampled with stool from three separate bowel movements over a period of one week, 7, 3 and 1 day(s) prior to colonoscopy, respectively (figure 1). On the g-FOBT test cards, two separate samples from different parts of the stool had to be applied using the enclosed cardboard sticks. The final test card for g-FOBT and the FIT were sampled with stool taken from the day before colonoscopy, and before bowel preparation had started. Illustrated instructions guided the participants to sample their stool ensuring that contact with water or urine was prevented. No restrictions were made with regard to either diet or use of medication during the week in which stool samples were taken.(20)

Figure 1: Study design



Test analysis

On the day of colonoscopy, both the completed FOBTs and the informed consent form were handed over to the nursing staff at the endoscopy-department. All FITs were stored at minus 5 degrees Celsius on arrival and all g-FOBTs were stored at room temperature according to

the manufacturers recommendations. Tests were analyzed according to the manufacturers instructions within one week by two experienced technicians, who were unaware of the clinical data.(21) Both technicians were tested negative for colour blindness and received special training for reading the test cards.
FIT samples were processed with the OC sensor MICRO desktop analyser (Eiken Chemical co, Tokyo, Japan).(21) A haemoglobin concentration of ≥ 100ng/ml was taken as cut off, according to the manufacturers recommendations. G-FOBT samples were considered positive when a blue colour appeared in at least 1 out of 3 test cards, following application of the reagent. Test cards were not rehydrated prior to analysis.

Colonoscopy
All participants underwent complete colonoscopy in one of five participating centres. Colonoscopies were performed, or supervised, by experienced gastroenterologists. Conscious sedation using Midazolam was offered to all patients. Endoscopists were blinded to the results of both tests. A complete colonoscopy was defined as intubation of the caecum with identification of the ileocecal valve or appendiceal orifice, or intubation up to an obstructing neoplasm.
In addition, patients with inadequate bowel cleansing, as judged by the individual endoscopist, were excluded as well. Patients were classified based on the most advanced lesion detected in their colon. Estimated size of all lesions, as reported in the colonoscopy report, were categorized.

Detected lesions
Histology of tissue samples obtained during colonoscopy was evaluated according to standard procedures. Pathology reports were collected centrally and entered into the database. Adenomas ≥1.0 cm, with any villous features (i.e. tubulovillous or villous adenoma) or high-grade dysplasia, were considered advanced adenomas.(22,23)Advanced neoplasia included all cases of colorectal cancer and all advanced adenomas. Colorectal carcinomas were staged according to the AJCC cancer staging manual.(24)

Statistical analysis
Defining colonoscopy outcome as gold standard, sensitivity and specificity of both FOBTs were calculated, for advanced adenomas and for CRC separately. Furthermore, these test characteristics were calculated for all participants with either one or more advanced adenoma(s) or an early stage carcinoma (AJCC stage I and II). Since both FOBTs were performed in parallel on the same stool samples, McNemar's test could be used for comparison of correlated proportions.

The sample size was predetermined, based on an anticipated difference in sensitivity for detection of colorectal cancer of 20% between Hemoccult II and OC-sensor. The enrolment

of 1650 participants was required, assuming a prevalence of colorectal cancer of at least 2,5% in this study population, to provide the study with a statistical power of 80% to detect a significant difference at a two-sided alpha level of 0.05 with the use of McNemar's test. All analyses were performed with SPSS for Windows Version 15 (SPSS Inc., Chicago, USA).

Results

Demographics
Overall 2217 individuals who underwent colonoscopy performed at least one of both FOBTs. In total 396 individuals were excluded for reasons listed in Table 1. The mean age of 1821 individuals that were included for final analysis was 59.6 years (range 18-86 years, 95% CI 59.0- 60.1). The majority of the subjects (56.9%) was female.

Indications for colonoscopy
The primary indication for colonoscopy was available for 1742 out of 1821 individuals. In 79 patients (4.3%), the primary indication remained unspecified. Indications were classified in four categories listed in Table 2. Almost half of the population (N=897, 49.3%) was referred for colonoscopy because of gastrointestinal symptoms and 44.3% of patients was asymptomatic and had an indication for screening or surveillance colonoscopy (N=807).

Table 1: Reasons for exclusion of 396 patients out of 2221 consecutive patients undergoing colonoscopy in five hospitals in the Amsterdam area.

Reason for exclusion		**N=396 (100%)**
Incomplete colonoscopy	Caecum not reached	102 (25.8%)
	Insufficient bowel lavage	27 (6.8%)
Documented history of IBD		77 (19.4%)
FIT not sampled		87 (22.0%)
g-FOBT not sampled		98 (24.7%)
Colostomy		5 (1.3%)

Table 2: Primary indications for colonoscopy among 1821 consecutive patients in five hospitals in the Amsterdam area enrolled in a study comparing FIT versus g-FOBT

Indication Group	Indication for colonoscopy	N
Symptomatic/suspect		
	Weightloss	15
	Clinical suspicion of diverticulitis	14
	Clinical suspicion of IBD	17
	Abdominal pain	280
	Anemia	77
	Hematochezia	190
	Altered bowel habits	304
	Clinical suspicion of CRC (inconclusive pathology)	1
	Colonoscopy for polypectomy	37
	Total	**935**
Screening & Surveillance		
	Average risk	32
	Familial history of CRC	288
	Lynch syndrome	29
	Polyp surveillance	314
	Post CRC surveillance	120
	Radiological suspicion of malignancy	21
	Total	**804**
Other		
	Not specified	**82**
	Grand total	**1821**

Colonoscopy results

In 194 of 1821 patients (10.7%), at least one advanced adenoma was found on colonoscopy. Adenocarcinomas were found in 62 of 1821 patients (3.4%). Of these, 28 (45.2%) were classified as early stage colorectal cancer (AJCC stage I and II) and 31 patients (50.0%) as late stage (AJCC stage III and IV). Three rectal cancers could not be accurately staged due to the effects of neo-adjuvant radiotherapy.

Test results

Overall positivity rate for the g-FOBT was 6.7% (122/1821) and for the FIT 11.8% (214/1821). The g-FOBT detected 46 of 62 cancers for a sensitivity of 74.2%, whereas the FIT detected 54 of 62 cancers, for a sensitivity of 87.1% (Table 3). FIT detected 7 cancers that did not score a positive g-FOBT. Only one cancer scored a positive g-FOBT but not a positive FIT. The observed difference in sensitivities between the two tests was significant (P=0.02). Sensitivity for screen relevant lesions (advanced adenomas and early stage cancers) was 23.0% for g-FOBT and 40.5% for FIT (P<0.001).(25) Yet, g-FOBT was found to have a higher specificity compared to FIT for cancers of all stages (95.7% vs. 91.0%, P<0.001) and for advanced adenomas (97.4% vs. 94.2%, P<0.001). The difference between sensitivities of g-FOBT and FIT for the detection of early or late stage colorectal cancers respectively, showed a similar trend but did not reach statistical significance. The sensitivities of g-FOBT and FIT for early stage cancers was 57.1% and FIT 75.0%, respectively (Table 4). For late stage cancers g-FOBT had a sensitivity of 87.1% and FIT 96.8%.

Table 3: Sensitivity and specificity of g-FOBT (Hemoccult II®) and FIT (OC-sensor®)§ for detection of advanced adenomas, advanced neoplasia, colorectal cancer (CRC), in a consecutive series of 1821 patients referred for colonoscopy.

	Advanced Adenomas *194/1821*	**Early stage CRC (Stage I&II) + Advanced Adenomas*** *222/1821*	**CRC** *62/1821*	**Advanced Neoplasia** *256/1821*
Sensitivity Hemoccult II® *(95% CI)*	**18.0 %** 35/194 *(12.9–24.2)*	**23.0 %** 51/222 *(17.6–29.1)*	**74.2 %** 46/62 *(61.5–84.5)*	**31.6 %** 81/256 *(26.0-37.7)*
Sensitivity OC-sensor® *(95% CI)*	**35.6 %** 69/194 *(28.9–42.7)*	**40.5%** 90/222 *(34.1 – 47.3)*	**87.1 %** 54/62 *(76.2–94.3)*	**48.1 %** 123/256 *(41.8-54.4)*
p-value**	<0.001	<0.001	0.02	<0.001
Specificity Hemoccult II® *(95% CI)*	**97.4 %** 1524/1565 *(96.5-98.1)*	**97.4 %** 1524/1565 *(96.5-98.1)*	**95.7 %** 1683/1759 *(94.6–96.6)*	**97.4 %** 1524/1565 *(96.5-98.1)*
Specificity OC-sensor® *(95% CI)*	**94.2%** 1474/1565 (92.9-95.3)	**94.2%** 1474/1565 (92.9-95.3)	**91.0 %** 1599/1759 *(89.5–92.2)*	**94.2%** 1474/1565 (92.9-95.3)
p-value**	<0.001	<0.001	<0.001	<0.001

**Of three rectal tumours the oncological stage of disease could not be assessed due to the effects of neo-adjuvant radiotherapy.*
***McNemar's test was used to compare paired proportions*
§ cut-off level ≥100 ng/ml

Discussion

In the present study, performance characteristics of both g-FOBT and FIT were evaluated in parallel in a referral population of 1821 patients who underwent complete colonoscopy. This design allowed to deal with two major issues that, thus far, have remained unaddressed. Firstly, in most studies so far on FIT, only individuals with a positive test underwent subsequent colonoscopy, which precluded the determination of false negativity rates and thus specificity of the investigated tests. Secondly, previous studies comparing g-FOBT and FIT did so mainly in separate patient groups, which limits determination of exactly which tumors are missed by one test but are detected by the other.

Overall, results of the present study are consistent with earlier observations in screening studies and confirm a significantly higher sensitivity of FIT for colorectal cancer as well as advanced adenomas. The referral population that was evaluated in the present study consisted of more individuals with CRC or advanced adenomas than an average risk screening population. Due to the relatively high tumor yield in the referral population in the present study, test results of FIT and g-FOBT could be stratified for early stage cancers (AJCC Stage I and II) and late stage cancers (Stage III and IV). Importantly, for the screen relevant neoplasia (i.e. advanced adenomas and early stage cancers taken together), FIT significantly outperforms g-FOBT in terms of sensitivity with 40.5% versus 23.0%, respectively. This is of special importance since population-based screening programs for CRC aim to detect this category of neoplasia

Table 4: Test outcome of g-FOBT (Hemoccult II®) and FIT (OC-sensor®)§ in 62 patients diagnosed with colorectal cancer at an early stage (n=28) and at a late stage (n=31)

	Hemoccult II®		OC-sensor®		
	Positive	**Negative**	**Positive**	**Negative**	**Total**
Early stage disease (Stage I & II)	**16** *(57.1%)*	**12** *(42.9%)*	**21** *(75.0%)*	**7** *(25.0%)*	**28**
Late stage disease (Stage III and IV)	**27** *(87.1%)*	**4** *(12.9%)*	**30** *(96.8%)*	**1** *(3.0%)*	**31**
AJCC stage unknown*	3	0	3	0	**3**
Total	**46** *(74.2%)*	**16** *(25.8%)*	**54** *(87.1%)*	**8** *(12.9%)*	**62** (100%)

** three rectal tumours could not be accurately staged due to the effects of neo-adjuvant radiotherapy.*
§ cut-off level ≥100 ng/ml

specifically. A trend in the same direction was observed in early stage cancers alone, with detection rates of 75.0% versus 57.1% for FIT and g-FOBT, respectively, but this did not reach statistical significance.

In a screening-naive population both early and late stage colorectal cancers, the so called prevalent cancers, will be detected in a range consistent with their respective prevalences. Therefore, in a first round of a screening program, overall CRC detection rates will be inflated by the prevalent advanced stage cancers. However, given the nature of the disease, with usual annual or biennial screening programs, in a second round of screening, less advanced cancers will be left in the population.(26) Therefore, the performance characteristics of the screening program will largely depend on the potential to detect early stage CRCs, i.e. incident cancers. In this respect, it is highly relevant that the present study allowed to analyze performance of both tests separately for early and late stage CRC. Preferably, these results need to be validated in a screening population, but the small numbers of CRCs detected in screening studies will hamper such a study design.

Positive and negative predictive values of a test are influenced by the prevalence of a disorder in the population that is tested. Therefore, in this referral population, these values were not calculated as they would not reflect predictive values in a screening population. However, sensitivity and specificity are characteristics of a diagnostic test and are not influenced by the prevalence of a disease in population.(27)
With respect to whether the present findings are generalizable to a screening population, it could be argued that preclinical (i.e. screen detected lesions) may be different (e.g. in their tendency to bleed) from symptomatic lesions. However, so far there is no evidence that either supports or falsifies this hypothesis.

The present study shows that the higher sensitivity of FIT goes at the cost of a somewhat lower specificity (advanced neoplasia; 97.4% versus 94.2%, overall cancer; 95.7% versus 91.0%, for g-FOBT and FIT, respectively). The higher specificity of g-FOBT compared to FIT, was recently described in another study comparing exactly the same g-FOBT and FIT, but in two separate populations.(8) In this study, that used a population screening design, specificity could not be calculated directly, since only FIT or g-FOBT positive individuals were offered colonoscopy. Hence specificities were calculated based on rare disease assumptions. This may explain the small differences in specificity between their study and the current one, in which all individuals underwent colonoscopy. Moreover, not all guaiac based FOBTs have the same test characteristics. The Hemoccult II used in the present study is a low sensitivity FOBT. The United States only endorse the use of sensitive g-FOBTs (e.g. Hemoccult Sensa) for screening and therefore the results might be different if an FOBT with better sensitivity was used.(28)

Apart from the higher sensitivity for screen relevant tumors, FIT has several other advantages. The technical characteristics of the FIT test used in the present study allow for automated analysis, unlike g-FOBT, which makes it suitable for high throughput application. Furthermore, patient acceptance of a test is a major determinant of compliance and consequently success of a screening program. The OC-sensor® has been found to be significantly better accepted by the average risk target population for colorectal cancer screening than the Hemoccult II®.(8) Finally, the reproducibility and quality control of FIT is good, where g-FOBT was not optimal.(29,30)

Secondary prevention of CRC is a major health care issue, and several countries already have introduced g-FOBT in large pilot-studies or nationwide colorectal cancer screening programmes.(31,32) A growing body of literature lends support to the notion that FIT is superior to g-FOBT in colorectal cancer screening.(8,15,17,33,34) The present study adds to this the observation that FIT has a significantly higher sensitivity for screen relevant tumors than g-FOBT. In addition, the present study allows for a more precise estimation of the specificity of FIT for colorectal tumors.

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